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Applicant: Hein et al.

Title: TRANSGENIC PLANTS
EXPRESSING ASSEMBLED
SECRETORY ANTIBODIES

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Art Unit: 1638

DECLARATION OF RICHARD LERNER, M.D., UNDER 37 C.F.R. § 1.132

I, Richard Lerner, hereby declare that:

1. I was educated in the biomedical sciences at Northwestern University and at Stanford University where at the latter, I received a B.S. and an M.D. degree. I interned at the Palo Alto Stanford Hospital and was a postdoctoral fellow in experimental pathology at the Scripps Clinic and Research Foundation. For the next thirty years, I have held various scientific positions at the now Scripps Research Institute, the world's largest, private non-profit biomedical research facility. During this time, I also held administrative leadership positions at Scripps, the most prominent being chairman of the Department of Molecular Biology from 1982-1986 and then president of the Scripps Research Institute. I have conducted research for over thirty years and am the author or co-author of over 370 published scientific articles in biomedical science. Many of the publications from the late 1980s and early 1990s deal with issues of antibody specificity and antibody expression. I have been a member of the editorial board of more than 10 scientific journals and have been an official reviewer for hundreds articles submitted for publication. A brief summary of my accomplishments and a recent copy of my Curriculum Vitae is attached as APPENDIX 1.

2. I am generally familiar with the work disclosed in the above-captioned patent application and am aware that claims from this application have been rejected by the Examiner as allegedly being obvious over a dissertation by Klaus During ("the During dissertation") of the University of Koln, FRG, carrying the date of July 1988. I am also familiar with the During dissertation (attached as APPENDIX 2),¹ which is poorly organized and quite difficult to read. My previous review of this document has been extended both in terms of scope and depth in order to assist the Examiner in evaluating During's alleged achievements from the perspective of the ordinary skilled artisan at the time period between the alleged publication date of During (i.e., July 1988) and what I have been informed is the earliest filing date of the above referenced patent application (i.e., October 27, 1989). Thus, before discussing the During dissertation, I will review the state of the art of immunoglobulin expression prior to October 27, 1989. As my analysis will demonstrate, there existed at the time of During a significant prejudice in the art against the possibility that plant cells were capable of processing and assembling an immunoglobulin with antigen specificity (i.e., an antibody molecule).

- I. **There was a significant prejudice in the art against the possibility that plant cells could successfully process and assemble an immunoglobulin with antigen binding specificity around the time of the During dissertation (i.e., circa 1988/1989).**

3. It was commonly known prior to October 27, 1989 that antibodies were naturally the product of specialized mammalian cells known as lymphocytes. It was also known that only a subset of lymphocytes, the B cells, produced antibodies. Natural antibodies comprise a four chain structure made up of two identical heavy chains of about 50,000 daltons each and two identical light chains of about 25,000 daltons each. It was appreciated by the early 1980s that the biology of antibody expression was complex and varied with the maturation state of the B cell. For example, it was known that the heavy

¹ The English translation which I reviewed bears the name "Ralph McElroy Translation Company, 910 West Avenue, Austin Texas, Job No: 1596-81522." All reference to pages in During are to this English translation.

and light chain genes were inherited as non-functional gene segments and that only functional heavy and light chain genes were formed by rearrangement in B cells. It was further appreciated that rearrangement of the heavy chain gene preceded that of the light chain gene and that in the earliest member of the B cell lineage, the pre-B cell, only the heavy chain gene was rearranged. Thus, in the pre-B cells, the heavy chain was produced intracellularly and was not transported to the cell surface or secreted. In young B cells where light chain has been productively rearranged, the light chain was synthesized along with the heavy chain and a full-sized immunoglobulin is formed and expressed on the cell surface. When young B cells encounter foreign antigen and receive the proper signals, the B cells mature into a plasma cell, which secretes or exports antibody to the extracellular medium.

4. This story of antibody expression in B cells is further complicated by the involvement of an additional protein called binding immunoglobulin protein or "BiP", discovered in the early 1980s. BiP is located in the endoplasmic reticulum of B cells and binds to heavy chain produced in pre-B cells. In young B cells, heavy chain also binds to BiP, but in the presence of light chain, the heavy chain is released from BiP and the two chains form a fully assembled antibody which is then exported to the cell membrane.² It was also known that unlike the case in pre-B cells, heavy chain production in the absence of light chain production was often fatal in mature B lymphocytes, a phenomenon known as heavy chain toxicity.³ Heavy chain toxicity was recognized by the absence of myeloma cell mutants that produced heavy but not light chains. Prior to October 1989, it was not clear why heavy chains were toxic to B cells.

5. Thus, it should be apparent from this review that by the later 1980s, immunoglobulin expression in B cells was regarded as a highly developed phenomenon which involved a complex interplay between heavy and light chain and other cellular proteins (e.g., BiP) which orchestrate the processing and export leading to secretion of immunoglobulin at various B cell maturation stages. Consequently, it was

² See e.g., Bole et al., *J. Cell Biology*, 102:1558-1566, 1986, APPENDIX 3; Hass et al., *Nature* 306:387-389, 1983, APPENDIX 4.

³ See e.g., Hass et al., *Proc. Natl. Acad. Sci. USA*, 81:7185-7188, 1984, APPENDIX 5, (p. 7185, left column).

commonly believed during the early to mid 1980s that immunoglobulin production was a highly specialized function that could only occur in B cells of mammals. As one author wrote:⁴

Because immunoglobulin production is a specialized function of cells of the B-lymphocyte lineage, it is expected that the conditions for proper Ig gene expression will be provided only in appropriate immunocompetant cells.

Such views were commonly held and reflected a prevailing strong prejudice through much of the 1980s against the possibility of using non-B cells to express antibodies.

6. As the commercial value of monoclonal antibodies became evident in the late 1970s and early 1980s, emphasis was placed on producing these antibodies through recombinant expression so that improved features could be engineered into the antibody molecule. Naturally, much effort was directed to achieving recombinant expression of antibodies in transformed B cells. However, a few individuals attempted to express an antibody in microorganisms that were previously used for expressing foreign proteins. Initial attempts to achieve heavy-light chain assembly in *E. coli* bacteria in the early 1980s were unsuccessful.⁵ In 1988, Better et al. obtained heavy-light chain assembly in the periplasmic space of *E. coli* by placing DNA encoding a bacterial signal sequence 5' to the mature sequence of the light and heavy chain encoding DNA.⁶ In 1985, Wood et al. demonstrated synthesis of a heavy and light chain, cleavage of the signal sequence and assembly into an antibody in extracts of the yeast, *Saccharomyces cerevisiae*.⁷ It was noted, however, that the yeast did not secrete active antibody into the culture medium and the majority of the antibody was in an insoluble fraction.⁸

⁴ Ochi et al, Proc. Natl. Acad. Sci. USA, 80:6351-6355, 1984, APPENDIX 6.

⁵ See Boss et al., Nucl. Acids Res. 12:3791-3806, 1984, APPENDIX 7; Cabilly et al., Proc. Natl. Acad. Sci. USA, 81:3273-3277, 1984, APPENDIX 8.

⁶ Better et al., Science 240:1041-1043, 1988), APPENDIX 9.

⁷ Wood et al., Science, 240:1041-1043, 1988, APPENDIX 10.

⁸ *Id.* at p.448, right column.

7. Despite the fact that some reports demonstrated antibody assembly in bacteria and yeast, it is my opinion that this would not have reduced the prevailing prejudice in the art that existed up to October 27, 1989 with respect to antibody assembly by plants. This is because plant cells were understood to be distinct from both mammalian cells and single cell microorganisms. For example, many differences between animals and plant cells were known, as summarized in the in the following commentary:⁹

However, in addition to their photosynthetic capacities, plants show important differences from animals that extend to the cellular level: For example, that vascular system of higher plants carries water, minerals absorbed by the roots, and carbohydrates being transported from sites of synthesis in green tissues to sites of use or storage. A variety of small molecules are also translocated including hormones. Unlike in higher animals, the extraceulluar fluids of the vascular system are not rich in macromolecules, nor is there an abundant population of circulating cells. Paralleling this, plant cell are surrounded by walls, into and out of the cells but severely restrict access of larger molecules to the cell surface and also limit the interactions of adjacent cells with one another. As with bacteria, the walls provide mechanical support so that plants can grow in fresh water, and multicellular forms can circulate a relatively dilute solution; the cells can resist osmotically induced pressures without bursting. These characteristics, plus the presence in the plant of vacuoles controlling ion distribution within the cell, produce balances of ion and water movements that can be quite different from the ones usually found in animal cells.

Although some procaryotes and fungi also have cell walls, plant cell walls are more complex and variable, providing additional functions not present in cell walls of other organisms. Furthermore, processes underlying signal sequence processing and protein secretion also were understood to be different between mammalian cells and plant cells.¹⁰

⁹ See Holtzman et al., *Cell & Organelles*, 3rd ed. 1984, CBS College Publishing, p.357-360, APPENDIX 11.

¹⁰ Duong et al., *J. Biol. Chem.* 262:6328-6333, APPENDIX 12, 6328-6329 ("Furthermore, the biological properties of one of the synthetic peptide analogs reveals differences in the nature of the mammalian versus the plant secretory apparatus.").

In addition, at the time of the During dissertation, it had not been demonstrated that plant cells contained a BiP protein or an analogue that would function equivalently.¹¹ My analysis, therefore, convinces me that a person of skill in the field of immunology or protein expression would have been prejudiced in the time frame up through October 27, 1989 against the possibility that plants could be used to assemble antigen binding immunoglobulins, despite the fact that success was observed in a few selected examples of unicellular microorganisms.

8. It should be apparent from the above that there was a sound basis for a real prejudice in the art against using plants to produce a processed and assembled immunoglobulin which is antigen specific around the time of the During dissertation (*circa* 1988/1989). Were this not the case, then Applicant's invention clearly would not have been roundly hailed in both the scientific literature and in the general press as a significant scientific discovery and medical breakthrough.¹² Because of this prejudice, the ordinary skilled artisan in 1988/1989 would have shown a good deal of skepticism when evaluating evidence supporting a claim of successful antibody assembly in plant cells and would not be convinced unless the proof was well founded. As will be discussed below, the proof supporting During's claims of successful immunoglobulin expression in plants is far below what was needed to overcome the prejudice in the art and reasonably convince one of ordinary skill that plants could be used to process and assemble an immunoglobulin with antigen binding specificity. In fact, During's antibody expression results are so contradictory and uncontrolled that they would not have been convincing even if there were no prejudice in the art.

II. The strategy for light chain and heavy chain expression adopted by During is different from that disclosed by the patent application in question.

9. The During dissertation describes an attempt to co-express the heavy and light chains of an IgM antibody known at B1-8 in plants. His strategy was to

¹¹ See Miernyk et al., J. Cell Biol., 197:abstract No. 4333, 1988, APPENDIX 13 (titled "Is there a BiP-like protein in the endoplasmic reticulum of plant cells?").

¹² See Cover page for Nature, volume 242(6245) and article published in the Los Angeles Times (San Diego County), November 2, 1989 (both attached as APPENDIX 14).

encode a leader sequence in front of the codons for the mature antibody chains. For the heavy chain leader, he introduced nucleic acid encoding the barley alpha amylase signal sequence directly in front of (5' to) the DNA encoding the amino terminal end of the heavy chain.¹³ During used the same amylase signal sequence for the light chain, but this time he included nucleic acid encoding three additional amino acids (Gly-Ser-Met) between the DNA encoding the leader sequence and the DNA encoding the amino terminus of the light chain (*Id.*). During, therefore, chose two distinct strategies for expressing each immunoglobulin chain.

10. The additional amino acids that would, through During's strategy, be encoded at the 3' end of the B1-8 light chain leader sequence were unusual in the context of known eukaryotic signal cleavage sites. At the time of During's dissertation, it was not clear what effect additional amino acids at the end of a leader sequence would have on final processing of the leader. Studies by the present Applicants as well as others in the art indicate that by introducing the amino acids Gly-Ser-Met between the C-terminal end of the leader and the first amino acid of the mature kappa chain, the structure of the potential cleavage site is altered.¹⁴

11. It is now clear from the art that mutations introduced in the vicinity of a cleavage site can adversely influence signal processing. This conclusion is based on analysis of many scientific reports, which address: 1) naturally occurring cleavage sites,¹⁵ and 2) the effect of mutation on the function of a cleavage site.¹⁶ During's strategy to include two polar amino acids (Gly-Ser) followed by a methionine residue to the cleavage site for the light chain leader likely obscured substrate recognition by disrupting structural determinants required for processing activity.¹⁷

¹³ During dissertation, APPENDIX 2, p18, top of page.

¹⁴ See Nielsen et al., Protein Engineering, 10:1-6, 1997, APPENDIX 15 (see abstract).

¹⁵ See references in APPENDIX 15-23 (see abstracts).

¹⁶ See references in APPENDIX 24-38 (see abstracts).

¹⁷ See Nielsen et al., Protein Engineering, 10:1-6, 1997, APPENDIX 15 (see abstract); Duffaud et al., J. Biol. Chem., 263:10224-10228, 1988, APPENDIX 39 (see abstract).

12. In addition, I conclude that During's strategy for mating the light chain leader to the mature light chain sequence cleavage site was likely subject to cleavage site ambiguity. This is reflected in statistical¹⁸ and neural network¹⁹ predictions of probable cleavage sites. For example, in all instances where Gly-Ser-Met is theoretically introduced distal to a cleavage site, an incorrect or absent cleavage site is predicted.²⁰ Whereas these computations are useful tools, they do not guarantee experimental success.²¹ As will be detailed further in my declaration, not surprisingly, the leader sequence strategy used by During did not demonstrate a clear experimental success. In view of the clear deficiencies of During's work, his claims of successful expression would not have been reasonably believed by the ordinary skilled artisan.

III. During's experimental evidence allegedly supporting heavy and light chain processing and assembly of an antigen-specific immunoglobulin is inconsistent and lacks in critical controls.

13. The During dissertation describes that plant cells were initially transfected with DNA encoding the antibody light chain but not the heavy chain. Incredibly, During was unable to detect light chain in the cells.²² The failure to detect expression of light chains would, in my opinion, have been disturbing to the ordinary skilled artisan because it was known that light chains can be readily expressed without heavy chains in B cells. In addition, a very low level of light chain expression would make it that much more difficult to detect heavy-light chain assembly. Furthermore, an increased relative heavy chain expression, which under the circumstances might be necessary to achieve assembly in view of the low levels of expressed light chain, conceivably could result in toxicity if plant cells turned out to be susceptible to heavy

¹⁸ See Von Heijne et al., APPENDIX 23 (see abstract).

¹⁹ See Nielsen et al., APPENDIX 15 (see abstract).

²⁰ See Nielsen et al., APPENDIX 15; Center for Biological Sequence Analysis, Dept. of Biotechnology, The Technical University of Denmark website (www.cbs.dtu.dk/; SignalP cleavage site predictor).

²¹ See Von Heijne et al., APPENDIX 23 (see abstract).

²² During dissertation, APPENDIX 2, p. 80, line 2 ("Repeated attempts to directly detect the light chain of B1-5 and for T4 lysozyme from the crude extract of tobacco mesophyll protoplasts were unsuccessful.").

chain toxicity as is the case for B cells.²³ Thus, During's failure to detect light chain expression in cells transformed to express only the light chain would have raised serious complicating issues requiring a more thorough investigation.

14. In spite of the failure to detect light chain expressed by itself, During proceeded to clone the heavy chain with the light chain into a dual cassette expression vector and attempted to express both chains in plant cells. Page 86-95 of the During dissertation contains the results and discussion related to detection of antibody expression which employed Western blotting and tissue printing (see section 3.14, pages 86 to 90) as well as ultrastructural analysis of transfected plant tissue (see section 3.16, pages 92-95). As indicated by the statement below, During understood that his expression system was suboptimal, and that if assembled antibody were produced, the amount would be very low relative to the total protein.²⁴

Due to the expected level of low percentage of sought protein in the total protein, sensitive detection methods had to be developed. For this purpose, a non-radioactive detection system, which is compatible with the system for DNA hybridization described in 2.7.5 and 3.3, was worked out for detection of proteins on nitrocellulose and Immobilon filters. . . .

A method therefore had to be developed that permits the sought protein to be enriched from the crude extract before Western blot or preferably to be isolated and concentrated to detectable concentration.

The acknowledged deficiencies of During's expression system ultimately forced him to develop a pre-enrichment scheme in order to apply Western blotting. Such scheme would have raised concern with the ordinary skilled artisan as to the overall credibility of During's findings because direct Western blotting was known to be extremely sensitive and had previously been used for demonstrating foreign host expression. Indeed, in contrast to During's inability to use direct Western blotting, assembled antibody generated in tobacco plants using Applicant's system as described in the above-captioned

²³ See Boyle et al, APPENDIX 3.

²⁴ During dissertation, APPENDIX 2, p.86, 2nd to last paragraph and 4th paragraph of p. 87.

patent application were readily detected by direct Western blotting (see Figure 5 of the above-captioned patent application). During's efforts to increase sensitivity creates a greater potential for artifactual results, requiring additional experimental controls. As will be evident below, During's experimental approach wholly fails to provide the additional controls.

15. To enrich for antibody in the plant extract prior to Western blotting, During exposed large volumes of plant extract to several rounds of affinity purification with CNBr activated Sepharose 4b to which is attached Ls136 antibody (monoclonal antibody allegedly specific for the light chain) or NP hapten.²⁵ Bound antibody (if present) was eluted, according to During, with 0.1 M glycine, pH 2.3 presumably for the Ls136-sepharose or NIP-cap for the NP-Sepharose.²⁶ During's Western blotting results are shown in Figure III/232 and discussed on page 89-90. During indicates that direct Western detection was unsatisfactory and that he could detect only "processed light chain" in the callus material through the pre-purified extracts.²⁷ During's statement appears to indicate that heavy chain detection was attempted, but was unsuccessful. I base this observation on the fact that During planned to detect heavy chain with an anti μ antibody by Western blotting²⁸ and because there were no results featured showing heavy chain detection. Thus, During fails to detect either the light or heavy chain in direct Western blotting but allegedly detects a "processed" light chain but not a heavy chain in the indirect (pre-processed) Western blots. To conclude as he does from the Western results that assembled B1-8 antibody was present in the plant extract, During must infer that which he is attempting to prove, that fully assembled antibody must have been present in the extract for light chain to have been enriched following binding to the NP hapten immunoabsorbent.²⁹ As will be seen below, this faulty circular

²⁵ During dissertation, APPENDIX 2, p. 87, 4th full paragraph through page 89, lines 11-13.

²⁶ During dissertation, APPENDIX 2, p.47, lines 7-10.

²⁷ During dissertation APPENDIX 2, p89, lines 3-4

²⁸ During dissertation APPENDIX 2, p.86, lines 12-13.

reasoning is open to alternative explanations which directly conflict with During's conclusion.

16. During's assertion of successful heavy-light assembly severely lacks the type of proof that normally would normally be required under the circumstances to draw such conclusion. Even accepting for the sake of argument During's detection of a "processed light chain" by indirect Western blotting, assembly still requires a heavy chain and During has no direct proof from either the direct or indirect Western that heavy chain was expressed. In fact, any of a number of artifacts may be the cause of During's Western results. For example, assuming for the sake of argument that a light chain was expressed by the plants, the NP hapten immunoabsorbents might have bound light chain even without heavy chain expression during the "enrichment" procedure. This is a real possibility because light chains alone have been known to exhibit a low but real affinity for antigen, particularly in circumstances such as the present case when the antigen is immobilized. Alternatively, light chains could have been purified by the immunoabsorbents if an endogenous plant protein existed which coincidentally had features in common with the heavy chain of the B1-8 antibody. Although I have no evidence that either of these scenarios were at play, they should (and could) have been eliminated by employing any of a number of possible controls. For example, During could have directly demonstrated that heavy chain was absolutely required for light chain binding during the pre-enrichment step. Alternatively, or in addition, During could have used biosynthetic radiolabeling of plant cells in combination with Western blotting to prove that a heavy chain was in fact co-enriched with light chain. This method is well known in the art and was previously used to demonstrate foreign protein expression.³⁰ Biosynthetic radiolabeling also helps to control for stripping of antibody during a low pH elution of an antibody immunoabsorbent column (i.e., the Ls136 adsorbent), a problem

²⁹ During dissertation APPENDIX 2, p.89, lines 14-17 ("By indirect detection of isolation of the functional antibody with hapten [and] detection of the light chain contained [there]in it could be demonstrated that plants are capable of synthesis of active monoclonal antibody whose individual chains are fused with a plant signal peptide.).

³⁰ See e.g., Rothstein et al., *Nature*, 308:662-665, 1984, APPENDIX 40, Fig. 2 (expression of wheat α -amylase in yeast cells labeled with ³⁵S-methionine).

encountered with CNBr.³¹ Since During employed low pH elution and CNBr linkage, he should have provided controls to address this potential problem.³²

17. During also evaluated antibody expression using "tissue printing," in which a leaf is pressed against a membrane in order to bind various proteins in the leaf to the membrane and the membrane is probed by the various immunological reagents used in Western blotting.³³ No extract is made in this case and no enrichment is used. In these experiments, During allegedly detected light chain, heavy chain and "aggregated B1-8," (the latter conclusion presumably is a result of Ac38 antibody binding to the tissue print). It is disturbing that During never even attempted to explain why heavy chain was detected in these experiments but not in the Western blots. In any event, even if he could explain this discrepancy in a scientifically acceptable manner, the tissue printing experiment inexplicably lacks the type of controls that are normally required to support the conclusions that During attempts to draw. The controls needed for tissue printing are the same types of controls typically employed in antibody binding assays such as ELISA or immunohistochemistry. As is always the case for antibody reagents (polyclonal or monoclonal), one must use antigen inhibition to validate the specificity of binding in each assay format (i.e. that binding is "antigen-specific"). For example, Gubler et al. demonstrated α -amylase secretion by plant cells by inhibiting tissue staining with antigen.³⁴ Similarly, Wood et al. used antigen inhibition to demonstrate B1-8 antibody assembly in yeast (the same antibody used by During).³⁵ In fact, Wood demonstrated that the NTP form of antigen inhibited better than the NP form of hapten, a well known signature of the B1-8 antibody.³⁶ The During dissertation evidences that During was

³¹ See Lihme et al., *J. Chromatography*, 376:299-305, 1986, APPENDIX 41, table 1.

³² Ls136 antibody which may have leached into the "enriched" leaf extracts may be detected by cross-reaction with the secondary reagents in the western blot.

³³ During dissertation, APPENDIX 2, paragraph bridging p.88 and 89.

³⁴ See Gubler et al., *Planta*, 168:447-452, 1986, APPENDIX 42, p448, right hand column (Specificity of antibody staining evaluated by using antibody previously absorbed with a 50 fold excess of antigen).

³⁵ Wood et al., APPENDIX 10, p448, right hand column, middle of page.

³⁶ Wood et al., APPENDIX 10, p448, right hand column, middle of page.

aware of the Wood et al. reference³⁷ and the heteroclitic nature of the B1-8 antibody,³⁸ but for reasons unknown to me, During failed to conduct any antigen inhibition controls. Sossountzov et al. studying immunogold localization of abscisic acid in plant tissues of *chenopodium polyspermum* L, likewise used an antigen inhibition control which the authors recognized as vital (my emphasis added to the following quote).³⁹

Preabsorbed ABA antibodies, which constitute an essential control for determining the specificity of the immunolabelling, produced less than one gold particle per μm^2 over cytoplasm, nucleic and plastids.

Although During diluted his antibody reagents with wildtype plant extract and still observed binding, this control is not sufficient to exclude other artifacts. For example, binding directed to insoluble antigens not present in the extract would not be inhibited in the presence of the extract.

18. The During dissertation includes immunogold electron microscopic analysis of the plant cells containing the dual heavy and light chain vector apparently using the same antibody reagents used in the Western blotting and tissue printing experiments. The dissertation describes that the Ac38 antibody (allegedly specific for a properly assembled B1-8 antibody) reacted with endoplasmic reticulum (ER) and chloroplasts in cells from induced plant stems.⁴⁰ Also described is that the Ls136 antibody (allegedly specific for light chains), reacted with cytoplasm, but not with ER or chloroplasts.⁴¹ Further described is the observation that none of the antibody reagents labeled in the vicinity of the plant cell wall or the intercellular space, and that no reaction with the golgi apparatus or vesicles were seen.⁴² During concludes without explanation that these experiments indicate "synthesis and assembling of a monoclonal

³⁷ During dissertation, APPENDIX 2, p.17, first full paragraph.

³⁸ During dissertation, APPENDIX 2, p.86, lines 21-23.

³⁹ Sossountzov et al, Planta, 168:471-481, 1986, APPENDIX 43 (p. 480, left hand column).

⁴⁰ During dissertation, APPENDIX 2, p. 94, first full paragraph ("Each chloroplast contains about 23-30 gold particles, often localized on thylakoid membranes").

⁴¹ During dissertation, APPENDIX 2, p.94, lines 7-10.

⁴² During dissertation, APPENDIX 2, p.94, lines 10-12.

B1-8 antibody . . . occur [sic] in the plant cells on the rough ER . . . ⁴³ If During's conclusion about successful B1-8 assembly in plant cells was correct, the Ac38 immunoreactivity would mean that assembled antibody, i.e., both a light chain and a heavy chain, were present in the ER and chloroplasts. Such conclusion, however, is inconsistent with During's own failure to observe light chain immunogold labeling of ER or chloroplasts. Furthermore, the chloroplastic reactivity by the Ac38 antibody is perplexing and During provides no explanation for why allegedly assembled antibody would be concentrated in such an organelle⁴⁴ I note that only weak immunogold labeling of chloroplasts was observed in During's plant cells expressing T4 lysozyme.⁴⁵

19. During's alleged success also is in conflict with the failure to detect by immunogold labeling, the Ac38 antibody or light chain reactive antibodies binding in the vicinity of the plant cell wall, the intercellular space, the golgi apparatus or vesicles.⁴⁶ In particular, the presence of processed and assembled immunoglobulin in B cells, or for that matter, protein expressed naturally by plants, was known to involve the golgi and/or vesicles. For example, ultrastructural analysis of immunoglobulin producing B cell lines by Newell et al., showed light chains in the golgi and assembled immunoglobulin in the ER, perinuclear space and/or golgi apparatus.⁴⁷ Others have reported that heavy and light chains are synthesized on separate membrane bound ribosomes and sequestered in the cisternae of the ER from which they are transported into the smooth membranes of the golgi apparatus.⁴⁸ Furthermore, ER and golgi staining was also previously observed for α -amylase in gibberellin-treated barley cells.⁴⁹ In contrast, During observed no golgi immunoreactivity using his light chain, heavy chain or Ac38

⁴³ During dissertation, APPENDIX 2, p.94, last paragraph.

⁴⁴ Chloroplastic targeting was known to require a special amino terminal transport peptide, something which to my knowledge has not been demonstrated in antibodies. Chloroplastic immunoreactivity was observed for abscisic acid but this is not a protein (see Sossountzov et al., APPENDIX 43).

⁴⁵ During dissertation, APPENDIX 2, p.97, line 1.

⁴⁶ During dissertation, APPENDIX 2, p.94, lines 10-12.

⁴⁷ Newell et al., British J. Haematology, 50:45-459, 1982, APPENDIX 44 (see abstract).

⁴⁸ Newell et al., APPENDIX 44 (see p.446).

⁴⁹ Gubler et al., APPENDIX 42, Fig. 2.

antibody reagents. cells were even capable of antibody assembly. Unusual results might be acceptable if plant cells were even capable of antibody assembly in unique and previously unknown ways, however, unusual results cannot make up for the lack of controls in other experiments.

20. The reliance During places on the Ac38 antibody to support his conclusions from the immunogold labeling is misplaced. The Ac38 antibody reacts with the Ac38 idiotype, an antigenic determinant expressed on cell surface immunoglobulin in the B cell population of C57BL/6 mice at very high frequency (around 1/1,000).⁵⁰ It was known, however, in the early 1980s that the majority of Ac38 idiotype bearing antibodies induced in C57BL/6 mice (by immunizing with Ac38 antibody) do not have NP binding specificity.⁵¹ This means that Ac38 antibody binding cannot be used to claim that NP antigen binding specificity is present, even if Ac38 binding were proven to be Ac38 idiotype specific by inhibiting binding with the specific antigen. Thus, even if During had done the proper antigen inhibition controls, he still could not use Ac38 antibody binding to infer that B1-8 light chain and heavy chain were properly processed and assembled resulting in NP antigen specificity. In any event, this issue is moot because During did not even perform the proper controls.

21. The During dissertation concludes that the ultrastructural immunogold results support the Western blotting results which together demonstrate synthesis and assembly of a monoclonal antibody in plants.⁵² Again, no reasoning to support this conclusion is provided and in my opinion, it is wholly unwarranted in view of the experimental difficulties such as the failure to detect the B1-8 heavy chain, and the lack of proper controls.

IV. Conclusion

⁵⁰ Dildrop et al., EMBO, 3:517-523, 1984, APPENDIX 45, p.517, right hand column.

⁵¹ Dildrop et al., APPENDIX 45, p517, right hand column ("The resulting Ac38-positive hybridomas are thus in the majority unreactive with the NP hapten.").

⁵² During dissertation, APPENDIX 2, p.94, last paragraph.

22. My analysis of the immunology and protein expression art, circa 1988/1989, convinces me that a person skilled in such art would not have reasonably believed that plant cells could be used to express a properly processed and assembled antibody molecule. My view is not altered by the limited reports of antibody assembly in single cell microorganisms because such organisms would not have been considered predictive in this context for a plant cell. The art, therefore, supports a prejudice against the possibility of using plant cells to process and assemble a functional antigen-specific immunoglobulin molecule. The During dissertation does not overcome this prejudice because of serious unexplained inconsistencies and the absence of critical controls. In fact, During's work is so deficient that I would make the same conclusion even if there were no prejudice to overcome. Much more was needed to exclude artifactual results, which are more likely to be present when one is working at the limits of detectability. Even in its best light, giving the During dissertation the full benefit of the doubt, I am convinced that the skilled artisan would not have believed During's claims of immunoglobulin assembly in plant cells. Although During was awarded a Ph.D. degree for his dissertation, I do not know what weight his dissertation committee gave to his antibody expression experiments versus his T4 lysozyme expression experiments. I am aware that During eventually published his antibody plant work in a peer-reviewed journal (i.e., *Plant Molecular Biology*) after the inventors of the above-captioned application first published their work.⁵³ In fact, During's publication in *Plant Molecular Biology* discusses the earlier publication by the inventors, Hiatt and Hein as a successful demonstration of antibody expression in plants.⁵⁴ In my opinion, During's antibody experiments would not have been published were they not supported by the earlier published success of inventors, Hiatt and Hein. Had During attempted to publish his work in a peer reviewed journal before Hiatt and Hein published their work, my extensive experience as a reviewer/editor of scientific journals leads me to conclude During's work would most likely have been rejected as inconclusive.

⁵³ During et al., *Plant Mol. Biol.* 15:281-293, 1990, APPENDIX 46.

⁵⁴ During et al., APPENDIX 46, p.291, right column.

23. I am convinced that the ability to process, assemble, and secrete antigen specific immunoglobulin in plants was not achieved prior to the disclosure by Hiatt *et al.*, (see, e.g., article in Nature⁵⁵ and in U.S. Patent No. 5,202,422). The inventors used a different strategy from During and achieved a significant level of expression, allowing detection of the assembled chains by direct Western blotting. Hiatt *et al.*, not During, was the first to convincingly demonstrate the ability of plants to support production of an antigen-specific immunoglobulin in a manner that overcomes the prejudice in the art.

24. It is also my opinion that the During dissertation is silent about the ability of plants to produce single polypeptide forms of an immunoglobulin. Such single polypeptide immunoglobulins generally comprise at least the antigen-binding portion of a heavy chain and the antigen binding portion of a light chain. A commonly known form of single polypeptide immunoglobulin is the single chain Fv (sFv) fragment, which comprises a heavy chain variable region, a light chain variable region, and a short peptide which links the two regions together. I could find nothing in the During dissertation that addresses expression of a single polypeptide form of immunoglobulin such as an sFv fragment. The deficiencies of the During dissertation which has been extensively discussed with respect to a dual chain immunoglobulin apply equally well if not better with a single polypeptide immunoglobulin; The heavy chain variable region in the case of the single polypeptide must still assemble with the light chain variable region portion in order to achieve an antigen specific immunoglobulin. Again it was the inventors of the above-captioned patent application, not During, who were the first describe assembly of a an antigen-specific sFv in plant cells.

25. The During dissertation also fails to teach how to successfully use plant cells to express a heavy chain or light chain polypeptide, but not both, in plant cells. As already discussed, During attempted light chain expression without the heavy chain (but not vice versa) but failed to detect light chains in the plant cells. During did not even attempt to express heavy chains by themselves in plant cells. In contrast, the

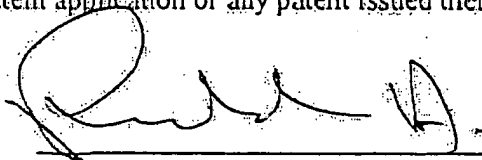
⁵⁵ Hiatt *et al.*, Nature, 342:76-78, 1989, APPENDIX 46.

inventors of the above-captioned patent application, were the first describe that plant cells can express the light chain or the heavy chain separately in a plant cell. In my opinion, the ability of plants to express each individual chain (light or heavy) was unexpected, particularly in the case of the heavy chain which was known at least in mature B cells to cause toxicity when expressed without a light chain.

26. I am aware that the Applicants, which I understand to be Andrew Hiatt and Mitch Hein, are inventors of several other pending patent applications in which the claims have been rejected over the During dissertation. I give permission to Applicants and their attorneys to file this declaration in support of any such other applications. In doing so, Applicants and their attorneys may replace the first page of the declaration with a substitute page that is otherwise the same except for the case caption information.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the captioned patent application or any patent issued therefrom.

3/11/02
Date


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Richard A. Lerner, M.D.

Dr. Richard A. Lerner's 30-year scientific career is particularly significant not only for the broad scope of his achievements in several diverse areas of biomedical research, but for his leadership and vision in concurrently directing the totality of scientific activities at The Scripps Research Institute, the country's largest private, non-profit biomedical research organization. His work spans a wide range of seemingly disparate discoveries, from unique insights into protein and peptide structure to the recent identification of a sleep-inducing lipid. He has been widely recognized by numerous prestigious societies and organizations in the U.S. and abroad.

One of his most recent accomplishments, and that for which he is perhaps most well known, is the groundbreaking work of converting antibodies into enzymes, permitting the catalysis of chemical reactions considered impossible to achieve by classical chemical procedures. While it has taken enzymes acting on natural biological systems millions of years of evolution to reach their present level of efficiency, antibodies can be produced overnight, for obtaining an almost limitless variety of products -- beyond natural ones -- with an efficiency that may exceed that of natural enzymes.

Dr. Lerner's prolific scientific output is accomplished with his simultaneous appointment as President of The Scripps Research Institute. His visionary leadership has kept the Institute at the frontier of science in several explicit and highly focused areas, giving the organization particular strength at the border between chemistry and biology. Emphasizing interdisciplinary collaboration that would be unlikely if not impossible at many major U.S. universities, Dr. Lerner embraces the notion of providing the faculty with a significant degree of freedom and the full range of technical resources to remain at the cutting edge. And recognizing the trend of shrinking Federal resources for science as far back as the early 1980s, Dr. Lerner has encouraged the formation of large-scale industrial collaboration agreements with major pharmaceutical industries, which have given the Institute the opportunity to recruit, build, expand, and remain state-of-the-art in facilities and instrumentation.

Dr. Lerner graduated from Northwestern University and Stanford Medical School. He interned at Palo Alto Stanford Hospital, and received postdoctoral training at Scripps Clinic and Research Foundation in experimental pathology. Since 1970 he has held staff appointments at Wistar Institute in Philadelphia and at the Research Institute of Scripps Clinic (renamed The Scripps Research Institute) in La Jolla. He served as Chairman of the Department of Molecular Biology of the Institute from 1982-1986 prior to assuming the presidency of the organization.

Dr. Lerner has received numerous prizes and awards, including the Parke Davis Award in 1978, John A. Muntz Memorial Prize in 1990, San Marino Prize in 1990, The Burroughs Wellcome Fund and the FASEB, Wellcome Visiting Professor Award in 1990,

The College De France Lectureship in 1991, Arthur C. Cope Scholar Award in 1991, The Tenth Annual Jeanette Piperno Memorial Award in 1991, Sixteenth Annual CIBA-GEIGY Drew Award in Biomedical Research in 1992, Humboldt Research Award in 1994, and the Wolf Prize in Chemistry in 1994-1995, the California Scientist of the Year Award in 1996, and the Coley Award for Distinguished Research in Basic and Tumor Immunology in 1999 .

In addition to Charter Membership in the American Society for Virology, Dr. Lerner holds memberships in the American Society for Experimental Pathology, American Society of Microbiology, New York Academy of Sciences, Biophysical Society, and the Pluto Society. He is on the editorial boards for the Journal of Virology, Molecular Biology and Medicine, Vaccine, In Vivo, Peptide Research, Bioorganic and Medicinal Chemistry Letters, Drug Targeting and Delivery, Senior Contributing Editor to PNAS and Chemistry and Biology, Bioorganic and Medicinal Chemistry, Molecular Medicine, Catalysis Technology and Angewandte Chemie.

Dr. Lerner was elected Foreign Member of the Royal Swedish Academy of Sciences in 1985; Member, National Academy of Science USA in 1991; Member, Scientific Policy Advisory Committee, Uppsala University, Uppsala, Sweden in 1991; Member, Scientific Advisory Board, Economic Development Board, Singapore in 1991; Trustee, The Neurosciences Research Foundation, Inc. in 1992; Member, Advisory Board, Chemical & Engineering News in 1994; Member, ETH Institute of Biotechnology Advisory Board, Zurich, in 1994; Member, Stanford Linear Accelerator Center Scientific Policy Committee, Stanford, CA., 1995-1998; Member, Center for Nanoscale Science and Technology Scientific Advisory Board in 1996; Member, College of Chemistry Advisory Board, University of California, Berkeley, 1996-1997; Member, California Council on Science and Technology Board of Directors, 1996-1997; Member, Advisory Steering Group for Chemistry, California State University, 1996; and Member, Academic Committee of the Board of Governors of Technion Israel Institute of Technology, 1998.

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Stanford University Medical School, B.S., M.D. 1959-1964
Internship, Palo Alto Stanford Hospital, 1964-1965

Professional Positions

1965 Research Fellow, Department of Experimental Pathology, Scripps Clinic and Research Foundation, La Jolla, California
1968 Associate, Wistar Institute, Philadelphia, Pennsylvania
1970 Associate, Department of Experimental Pathology, Scripps Clinic and Research Foundation, La Jolla, California
1972 Associate Member, Department of Experimental Pathology, Scripps Clinic and Research Foundation, La Jolla, California
1974 Member, Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California
1977 Member, Department of Cellular and Developmental Immunology, research Institute of Scripps Clinic, La Jolla, California
1980 Head, Committee for the Study of Molecular Genetics and Member, Department of Immunopathology, Research Institute of Scripps Clinic, La Jolla, California
1982 Member, Department of Molecular Biology, Research Institute of Scripps Clinic, La Jolla, California
1982 Chairman, Department of Molecular Biology, Research Institute of Scripps Clinic, La Jolla, California
1988 Professor, Department of Chemistry, Research Institute of Scripps Clinic, La Jolla, California
1987 Director, Research Institute of Scripps Clinic, La Jolla, California
1991 President, The Scripps Research Institute, La Jolla, California
1996 Member, Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, California

SOCIETIES AND BOARDS

Member Phi Eta Sigma
Member Alpha Omega Alpha
Member American Society of Nephrology
Member American Association of Immunologists
Member American Society for Experimental Pathology
Member American Society of Microbiology
Member New York Academy of Sciences
Member Biophysical Society
Chairman, International Symposium on the Molecular Basis of Cell-Cell Interaction (1977)
Consultant, Special Virus Cancer Program, National Cancer Institute
Ad hoc Member of Molecular Biology Study Section
Member Pluto Society
Fellowship Screening Committee of the California Division, ACS
Charter Member, American Society for Virology
Member Institute of Medicine Ad hoc Committee of New Research Opportunities in Immunology, National Academy of Sciences
Member Organizing Committee for "Modern Approaches to Vaccines", Cold Spring Harbor (1983)
Member Cancer Preclinical Program Project Review Committee, National Cancer Institute
Member Scientific Policy Advisory Committee, Uppsala University, Uppsala Sweden (1991)
Member Scientific Advisory Board Economic Development Board, Singapore (1991)
Member National Academy of Science, USA (1991)
Trustee, The Neurosciences Research Foundation, Inc. (1992)
Member Advisory Board Chemical and Engineering News, Washington, DC (1994-1996)
Member ETH Institute of Biotechnology Advisory Board, Zurich Switzerland (1994)
Member Stanford Linear Accelerator Center Scientific Policy Committee, Stanford, CA (1995-1998)
Member Center for Nanoscale Science and Technology Scientific Advisory Board, Houston, Texas (1996)
Member College of Chemistry Advisory Board, University of California, Berkeley, Berkeley, CA (1996)
Member California Council on Science and Technology Board of Directors, Newport Beach, CA (1996-1997)
Member, Advisor Steering Group for Chemistry, California State University, Los Angeles, Los Angeles, CA (1996)
Member, Editorial Advisory Board for the American Peptide Society Journal, Tucson, Arizona (1997)
Member, Academic Committee of the Board of Governors of Technion-Israel Institute of Technology, Haifa, Israel (1998)
Member, Editorial Advisory Board for Accounts of Chemical Research Journal, Los Angeles, CA (1998-2001)
Member, International Board of Governors, The Peres Center for Peace, Tel Aviv, Israel (1998)
Chairman, Governor's Council on Bioscience, Governor Gray Davis, Sacramento, CA (1999)

Member, The U.S. Department of Energy Biological and Environmental Research Advisory Committee, Washington, DC (1999).

Member, American Academy of Arts and Sciences, Cambridge, MA (2000)

HONORS and PRIZES

- | | |
|---------|---|
| 1970 | NIH AID Career Development Award |
| 1978 | Parke Davis Award |
| 1985 | Elected Foreign Member, The Royal Swedish Academy of Sciences |
| 1986 | Recipient of Lita Annenberg Hazen Professor of Immunochemistry |
| 1986 | Decorated as oficial de La Orden de San Carlos by the President of Colombia |
| 1989 | Cecil H. and Ida M. Green Chair in Chemistry |
| 1990 | Honorary Doctorate of Medicine, Karolinska Institute |
| 1990 | John A. Muntz Memorial Prize, Albany Medical College, New York |
| 1990 | San Marino Prize, Republic of San Marino |
| 1990 | The Burroughs Wellcome Fund and the FASEB Wellcome Visiting Professor Award in Basic Medical Science |
| 1991 | The College De France Lectureship, College De France, Paris |
| 1991 | Arthur C. Cope Scholar Award in Chemistry, Washington, D.C. |
| 1992 | CIBA-Geigy Drew Prize in Chemical Science, Drew University, Madison, New Jersey |
| 1993 | Hyp J. Dauben Award in Chemistry, University of Washington, Seattle, Washington |
| 1994 | Humboldt Research Award, Bonn Germany |
| 1994/95 | The Wolf Prize in Chemistry |
| 1996 | California Scientist of the Year Award |
| 1999 | William B Coley Award for Distinguished Research in Basic and Tumor Immunology, Cancer Research Institute, New York, NY |
| 1999 | Windaus-Medal/Award, Georg-August-Universität Göttingen, Göttingen Germany |

LECTURESHIPS

- | | |
|------|--|
| 1984 | Casper Wistar Lecture, The Wistar Institute, Pennsylvania. |
| 1986 | Fourteenth Peter Anthony Leermakers Symposium, Wesleyan University, Connecticut. |
| 1988 | The Thirteenth Annual B.R. Baker Memorial Lecture University of California, Santa Barbara, California. |
| 1988 | Allied Corporation Lecture, Rutgers University, New Jersey. |
| 1988 | 10th Annual Jim Mc Ginnis Memorial Lecture, Duke University, North Carolina. |
| 1988 | Selected to give the address on the occasion of Michael Heidelberger's 100th Birthday, New York University, N.Y. |

- 1988 Clark Lecture, San Jose State University, California.
- 1988 Dow Chemical Matrix Lecture, Midland, Michigan.
- 1988 Abbott Lecture, Brandeis University, Waltham, Massachusetts.
- 1989 Rennebohm Lecture, University of Wisconsin, Wisconsin.
- 1989 Mobay Lecture, University of Pittsburgh, Pittsburgh, PA.
- 1989 Spink Lecture, University of Minnesota, Minnesota.
- 1990 Smith Kline Lecture, Yale University, Connecticut.
- 1990 The John A. Muntz Lecture, Albany Medical College, Albany, N.Y.
- 1990 The First Josef Fried Symposium, University of Chicago, Illinois.
- 1991 Wallace P. Rowe Symposium, National Institute of Health, Bethesda, Maryland.
- 1991 The Mabel Beckman Lectures in Technologies, Stanford University, Stanford, California.
- 1991 Bruce Merrifield's 70th Birthday Symposium, Rockefeller University, New York, NY.
- 1991 Lilly Symposium, New York, NY.
- 1991 Peter Reichard Symposium, Stockholm Sweden.
- 1991 John G. Reinhold Lecture, University of Pennsylvania, Pennsylvania.
- 1991 The Tenth Annual Jeanette Piperno Memorial Award, Temple University, Philadelphia, Pennsylvania.
- 1992 Schering Lectures, Schering, Berlin, West Germany.
- 1992 Biomega Lectures in Organic Chemistry, McGill University, Montreal, Quebec, Canada.
- 1992 Seventh Annual William S. Johnson Symposium in Organic Chemistry, Stanford University, Stanford California.
- 1992 Sixteenth Annual CIBA-GEIGY Drew Award in Biomedical Research, Drew University, Madison, New Jersey.
- 1993 The John Howard Appleton Lecture in Chemistry, Brown University, Providence, Rhode Island.
- 1993 August-Wilhelm-von-Hofmann-Lecture, Gesellschaft Deutscher Chemiker, Germany.
- 1994 Lemieux Lecture, University of Alberta, Edmonton, Canada.
- 1995 Bender Lectureship in Chemistry, Northwestern University, Evanston, Illinois.
- 1995 Alfred Burger Lecturer in Chemistry, University of Virginia, Charlottesville, Virginia.
- 1996 Ephraim Katzir's 80th Birthday Symposium, The Israel Academy of Sciences and Humanities, Jerusalem, Israel
- 1996 Falk-Plaut Lecture, Columbia University, New York, NY.
- 1996 Debye Lectures, Cornell University, New York, NY.
- 1996 Harvey Lecture, The Rockefeller University, New York, NY.
- 1996 Honors Program Lecture, New York University School of Medicine, New York, NY.
- 1997 The Twelfth Biennial Carl S. Marvel Symposium, University of Arizona, Tucson, AZ.
- 1997 John and Dolores Stille Science Symposium, Colorado State University, Fort Collins, Colorado.

- 1997 Roma Eisenstark Memorial Lecture in Cancer Research, University of Missouri-Columbia, Columbia, MO.
- 1997 Arrhenius Lecture in Chemistry, Stockholm University, Stockholm, Sweden.
- 1998 Zeneca Pharmaceuticals Distinguished Lecturer in Chemistry, Wilmington, Delaware.
- 1999 Twenty-Seventh Annual Verna and Marrs McLean Science and Society Lecture in Biochemistry, Baylor College of Medicine, Houston, Texas.
- 1999 21st Oliver H. Lowry Lecture, Washington University School of Medicine, St. Louis, Missouri.
- 1999 Adolf-Windaus-Gedächtnis-Lecture, Georg-August-Universität Göttingen, Göttingen Germany.
- 2000 Rodney Porter Memorial Lecture, University of Oxford, Oxford, UK.
- 2000 Beverly and Raymond Sackler Lecture, Memorial Sloan-Kettering Cancer Center, New York, NY.
- 2000 Sumner Lecture, Cornell University, Ithaca, NY.
- 2001 18th Herbert C. Brown Lecture, Purdue University, West Lafayette, IN.
- 2001 Linus Pauling Lecture at the Centennial Celebration, California Institute of Technology, Pasadena, California.

Editorial Boards:

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11. Lerner, R.A., J.J. McPhaul, Jr. and F.J. Dixon. Soluble glomerular basement membrane (GBM) antigens in normal urine. Possible autoimmunogens in man. *Annals of Int. Med.* 68:249, 1968.
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